



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

✓ AF\$ 2600

In re application of:

Mack J. Schermer, et al.

Serial No.: 09/354,500

Filed: July 16, 1999

Group Art Unit: 1631

Examiner: Allen, Marianne P.

For: METHOD AND SYSTEM FOR AUTOMATICALLY CREATING CROSSTALK-CORRECTED DATA OF A MICROARRAY

Attorney Docket No.: PBS 0102 PUS

**APPEAL BRIEF**

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Sir:

This is an appeal brief from the final rejection of claims 1-18 of the Office action dated December 24, 2002. This application was filed on July 16, 1999.

**I. REAL PARTY IN INTEREST**

The real party in interest is Packard Bioscience Company, a corporation organized and existing under the laws of the state of Delaware, and having a place of business at 800 Research Parkway, Meriden, Connecticut 06450 as set forth in the assignment recorded in the U.S. Patent and Trademark Office on October 16, 2001 at Reel 012276/Frame 0703.

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## **II. RELATED APPEALS AND INTERFERENCES**

There are no appeals or interferences known to appellants, the appellants' legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

## **III. STATUS OF CLAIMS**

Claims 1-18 are pending in this application. Claims 1-18 have been rejected and are the subject of this appeal.

## **IV. STATUS OF AMENDMENTS**

An amendment to the non-final rejection dated July 8, 2002 was filed on October 1, 2002, and has been accepted for entry. There are no amendments pending in the present application.

## **V. SUMMARY OF THE INVENTION**

In one embodiment, the present invention provides a method for automatically creating crosstalk-corrected data of a microarray wherein crosstalk is caused by overlapping dye emission spectra, the method comprising providing a microarray substrate having three or more calibration dye spots, each of the calibration dye spots comprising a single pure dye, for each of the calibration dye spots, generating a dye image containing at least one of the calibration dye spots for each of a plurality of output channels, for each of the calibration dye spots, measuring an output of each of the output channels to obtain output measurements, computing a set of correction factors from the output measurements, and applying the set of correction factors to quantitation data obtained from the generated microarray images

containing spots having three or more dyes with excitation or emission spectra to obtain crosstalk-corrected data. (See, for example, Figures 5-8, and the specification on page 6, l. 4 through page 9, l. 12).

In another embodiment, the present invention provides a system for automatically creating crosstalk-corrected data of a microarray wherein crosstalk is caused by overlapping dye emission spectra, the system comprising a microarray substrate having three or more calibration dye spots, each of the calibration dye spots comprising a single pure dye, an imager having a plurality of output channels wherein for each of the calibration dye spots the imager generates a dye image containing at least one of the calibration dye spots for each of the output channels, means for measuring an output of each of the output channels for each of the calibration dye spots to obtain output measurements, means for computing a set of correction factors from the output measurements, and means for applying the set of correction factors to quantitation data obtained from the generated microarray images containing spots having three or more dyes with excitation or emission spectra to obtain crosstalk-corrected data. (See, for example, Figures 5-8, and the specification on page 6, l. 4 through page 9, l. 12).

## VI. ISSUES

1. Claims 1-18 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The first issue is whether claims 1-18 are described in the specification under 35 U.S.C. § 112, first paragraph.

2. Claims 1-18 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. The second issue is whether claims 1-18 are indefinite under 35 U.S.C. § 112, second paragraph.

3. Claims 1-18 were rejected under 35 U.S.C. § 103(a) as being unpatentable over either of U.S. Patent No. 5,578,832 to Trulson, et al. (hereinafter Trulson) or U.S. Patent No. 5,807,522 to Brown, et al. (hereinafter Brown) in view of U.S. Patent No. 6,225,636 to Ginestet (hereinafter Ginestet). The third issue is whether the Examiner has made a *prima facie* case that claims 1-18 are unpatentable under 35 U.S.C. § 103(a) over Trulson or Brown in view of Ginestet.

## **VII. GROUPING OF CLAIMS**

Claims 1-18 stand or fall together.

## **VIII. ARGUMENT**

### **1. The Examiner Has Failed to Make a *Prima Facie* Case That Claims 1-18 Are Unpatentable Under 35 U.S.C. § 112, First Paragraph**

The Examiner has rejected claims 1-18 as being unpatentable under 35 U.S.C. § 112, first paragraph. The Examiner asserted that "[t]his is a new matter rejection." (See, Final Office action dated December 24, 2002 on page 2, l. 10). However, the Examiner has failed to establish that claims 1-18 fail to meet the requirements of 35 U.S.C. § 112, first paragraph and the rejection should, therefore, be reversed. In that regard,

The first paragraph of 35 U.S.C. 112 requires that the "specification shall contain a written description of the invention..." This requirement is separate and distinct from the enablement requirement. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991).

...

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). (Manual of Patent Examining Procedure (MPEP), 8th Edition, August 2001, revised February 2003, § 2163, I.).

The Examiner contended “[t]he basis for the limitation ‘quantitation data’ is not present in the specification. The basis pointed to is the abstract. As such, the specification is objected to for failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o).” (See, Advisory Action dated March 25, 2003, page 2, ll. 1-3). However, the Examiner has failed to take proper notice of the teaching of the Abstract. In particular, “the abstract of the disclosure has been interpreted to be a part of the specification for the purpose of compliance with paragraph 1 of 35 U.S.C. 112.” (MPEP § 608.01(b), citing *In re Armbruster*, 512 F.2d 676, 678-79, 185 USPQ 152, 154 (CCPA 1975); see, also, *Hill-Rom Co., Inc. v. Kinetic Concepts, Inc.*, 209 F.3d 1337, 1341, 54 USPD2d 1437, 1440, n. 1 (Fed. Cir. 2000)). Furthermore, computer 52 is clearly identified as a quantitation computer (i.e., a computer to perform quantitation in accordance with the present invention). (See, specification on page 6, ll. 17-18). As such, the limitation “quantitation data” is fully supported by the specification and the rejection should be withdrawn.

**1. The Examiner Has Failed to Make a *Prima Facie* Case That  
Claims 1-18 Are Unpatentable Under 35 U.S.C. § 112, Second Paragraph**

The Examiner has rejected claims 1-18 as being unpatentable under 35 U.S.C. § 112, second paragraph. However, the Examiner has failed to establish that claims 1-18 fail to meet the requirements of 35 U.S.C. § 112, second paragraph and the rejection should, therefore, be reversed.

In that regard, "If the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. 112, second paragraph would be appropriate." (MPEP § 2131, citing *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993)).

The Examiner contended that "[i]t can not be determined from the specification what the metes and bounds of 'quantitation data' are. There does not appear to be a discussion or definition of what was intended to be encompassed or excluded." (see, final Office action dated December 24, 2002 on page 3, ll. 16-18). In response, Applicants provided the Examiner a copy of Schena, M., DNA Microarrays: A Practical Approach, April, 1999, page 12 which states, "Quantitation is usually accomplished by superimposing a grid over the microarray image and computing an average intensity value for each microarray element with automated software", and Schena, M., Microarray Biochip Technology, January, 2000, page 13 which states, "Data quantitation packages...and other commercial tools perform this function well. Typically, a user-defined gridding pattern is overlaid on the image, and the areas defined by the regular pattern of circles or squares are subjected to data extraction"., and page 179 which states, "After the spot location is determined in the image, a small patch around that location (target region) can be used to quantitate the spot intensity level." (See, response mailed March 13, 2003).

Furthermore, Applicants' representative conducted a search of the U.S. Patent and Trademark Office Patent Full-Text and Image Database on August 20, 2003 using the search parameters: SPEC/"quantitation data". The search yielded a total of 92 issued U.S. patents containing the term "quantitation data" in the specification and 56 of those patents issued prior to the filing date of the present application (i.e., prior to July 16, 1999). As such, the term "quantitation data" was clearly well known by one of ordinary skill in the art at the time the invention was made.

The Examiner has further asserted, "contrary to applicant[s'] arguments in the prior Office action as to what this limitation means, the abstract does not support that definition. The limitation adds no structural or functional feature to the claims as the claim always required quantitation of data in order to apply correction factors... The rejection under 112, 2<sup>nd</sup> paragraph in view of applicant[s'] assertion in the prior Office action as to its meaning. This term is not defined in the specification and thus its plain must have been intended and no particular type or method of quantitation is required or excluded by the claim language." (See, Advisory Action dated March 25, 2003, page 2, ll. 4-9).

However, "A claim term means 'what one of ordinary skill in the art at the time of the invention would have understood the term to mean.'" (See, for example, *Markman v. Westview Instruments, Inc.*, 52 F. 3d 967, 986, 34 USPQ2d 1321, 1335 (Fed. Cir. 1995) (en banc), *aff'd* 517 U.S. 370 (1996)). Therefore, based on the definition provided to the Examiner in the response mailed March 13, 2003 and the demonstrated use of the term "quantitation data" in at least 56 issued U.S. patents, the meaning of quantitation as would have been understood by one of ordinary skill in the art at the time of the invention such that the metes and bounds of the claim so as to understand how to avoid infringement has been provided. Furthermore, as argued above and contrary to the Examiner's assertion, the term 'quantitation data' is fully supported in the specification. As such, the Examiner has failed to establish that claims 1-18 fail to meet the requirements of 35 U.S.C. § 112, second paragraph and the rejection should, therefore, be reversed.

**3. The Examiner Has Failed to Make a *Prima Facie* Case That  
Claims 1-18 Are Unpatentable Under 35 U.S.C. § 103(a)  
Over Either of Trulson or Brown in View of Ginestet**

The Examiner has rejected claims 1-18 as being obvious under 35 U.S.C. § 103(a) over either of Trulson or Brown in view of Ginestet. However, the Examiner has failed

to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a) and the rejection should, therefore, be reversed. In that regard:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure.

MPEP § 2143 (citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Furthermore, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02 (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)).

Trulson provides methods and systems for detecting a labeled marker on a sample located on a support. (Trulson, Abstract). Brown is directed to a method an apparatus for forming microarrays on a support. (Brown, Abstract). Ginestet concerns multifluor-fluorescence in-situ hybridization (M-FISH) techniques using multiple multiband filters with image registration. (Ginestet, Title).

Independent claims 1 and 10 make it clear that the set of correction factors are applied to quantitation data obtained from generated microarray images containing spots having three or more dyes with excitation or emission spectra to obtain cross-talk corrected data. The Examiner concedes that this feature is neither taught, disclosed or discussed by any of the prior art references of record taken either alone or in combination with one another. (See, final Office action dated December 24, 2002 on page 3, ll. 6-8). Therefore, the Examiner has



failed to make a *prima facie* case of obviousness as is required under 35 U.S.C. § 103 and the rejection should be reversed.

Instead, the Examiner asserts “the claim amendment does not appear to exclude the image analysis of Trulson and/or Brown. Trulson and Brown establish that use of fluorescent dyes with cross-talk correction have been well known to those of ordinary skill in the art.” (See, final Office action dated December 24, 2002 on page 3, ll. 7-10). However, the presently pending independent claims provide for applying a set of correction factors to quantitation data obtained from generated microarray images containing spots having three or more dyes with excitation or emission spectra to obtain crosstalk-corrected data. To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP § 2143). The Examiner has failed to provide evidence that the cited references, alone or in combination, provide for the presently claimed invention, and to the contrary, the Examiner acknowledged that the claimed limitations distinguishes the invention over the prior art. As such, the rejection should be reversed.

The Examiner has also used impermissible hindsight to combine the teachings of Trulson or Brown and Ginestet to attempt to piece together the Applicants’ invention. The teaching or suggestion to make the claimed combination must be found in the prior art, not in the applicant’s disclosure. (See, MPEP § 2143; *see also, In re Dembiczak*, 175 F.3d at 999 (“Combining prior art references without evidence of ... suggestion, teaching, or motivation simply takes the inventor’s disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight.”)). Here, the Examiner urges that one would have been motivated to use matrix algebra for the correction factors disclosed by Ginestet, and Trulson explicitly suggests using more than two dyes. (See, final Office action dated December 24, 2002 on page 3, ll. 10-12). However, the presently pending independent claims provide for applying a set of correction factors to quantitation data obtained from generated microarray images containing spots having three or more dyes with excitation or emission spectra to obtain

crosstalk-corrected data. Even using impermissible hindsight, the Examiner has failed to piece together reference art that teaches the presently pending invention. As such, the Examiner has failed to make a *prima facie* case of obviousness as is required under 35 U.S.C. § 103 and the rejection should be reversed.

Moreover, “[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.” *Ecolochem, Inc. v. Southern Edison Co.*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) (citing *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 880 (Fed. Cir. 1998)). Here, the Trulson, Brown and Ginestet references cited by the Examiner fail to recognize the problem addressed by the Applicants’ claimed invention (i.e., as stated in the presently pending application on page 2, ll. 13-24, “To be accurate, the reader must be able to quantitate the brightness of each microarray spot for each labeled DNA sample used in the experiment”). Trulson, Brown and Ginestet fail to teach applying a set of correction factors to quantitation data as presently claimed. As such, the cited references, alone or in combination fail to address the problem addressed by the present invention. As such, the Examiner has failed to make a *prima facie* case of obviousness as is required under 35 U.S.C. § 103.

Regarding claims 2-9 and 11-18, which depend from claims 1 and 10, Applicants contend that these claims are patentable for at least the same reasons that claims 1 and 10 are patentable. Moreover, Applicants contend these claims recite further limitations, in addition to the limitations of claims 1 and 10, which render these claims additionally patentable over Trulson or Brown and Ginestet, alone or in combination.

## **IX. CONCLUSION**

The Examiner has failed to establish that claims 1-18 fail to meet the requirements of 35 U.S.C. § 112, first paragraph and the rejection should, therefore, be reversed. In particular, the term "quantitation data" is fully supported in the specification.


The Examiner has failed to establish that claims 1-18 fail to meet the requirements of 35 U.S.C. § 112, second paragraph and the rejection should, therefore, be reversed. In particular, the term "quantitation data" as used in the present invention has been defined such that a person of ordinary skill in the art could interpret the metes and bounds of the claims so as to understand how to avoid infringement.

The Examiner has failed to establish that claims 1-18 are unpatentable under 35 U.S.C. § 103(a) as being obvious over either of Trulson or Brown in view of Ginestet and the rejection should, therefore, be reversed. In particular, the Examiner has failed to provide evidence that the cited references, alone or in combination, provide the features of the present invention. In fact, the Examiner has conceded that the present invention is distinguished over cited references. Therefore, the final rejection of claims 1-18 should be reversed.

The fee of \$320 as applicable under the provisions of 37 C.F.R. § 1.17(c) is enclosed. Please charge any additional fee or credit any overpayment in connection with this filing to our Deposit Account No. 02-3978. A duplicate of this notice is enclosed for this purpose.

Respectfully submitted,

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Enclosure - Appendix

**IX. APPENDIX - CLAIMS ON APPEAL**

1                   1.     A method for automatically creating crosstalk-corrected data of a  
2 microarray wherein crosstalk is caused by overlapping dye emission spectra, the method  
3 comprising:

4                   providing a microarray substrate having three or more calibration dye spots,  
5 each of the calibration dye spots comprising a single pure dye;

6                   for each of the calibration dye spots, generating a dye image containing at least  
7 one of the calibration dye spots for each of a plurality of output channels;

8                   for each of the calibration dye spots, measuring an output of each of the output  
9 channels to obtain output measurements;

10                  computing a set of correction factors from the output measurements; and

11                  applying the set of correction factors to quantitation data obtained from the  
12 generated microarray images containing spots having three or more dyes with excitation or  
13 emission spectra to obtain crosstalk-corrected data.

1                   2.     The method as claimed in claim 1 wherein the step of generating includes  
2 the step of imaging the calibration dye spots to produce a dye image for each calibration dye  
3 spot.

1                   3.     The method as claimed in claim 1 wherein the substrate is a glass slide.

1                   4.     The method as claimed in claim 1 wherein each of the channels is  
2 optimized for a different dye.

1                   5.     The method as claimed in claim 1 wherein the step of generating is  
2 performed by an imager.

1                   6.     The method as claimed in claim 1 wherein each of the dyes is a  
2     fluorescent dye.

1                   7.     The method as claimed in claim 1 wherein the step of computing includes  
2     the step of computing crosstalk ratios based on spot brightness values for each of the  
3     calibration dye spots on each of the output channels.

1                   8.     The method as claimed in claim 1 wherein the number of calibration dye  
2     spots is more than or equal to the number of dyes.

1                   9.     The method as claimed in claim 1 wherein the calibration dye spots are  
2     hybridized target DNA and fluorescently labeled probe DNA.

1                   10.    A system for automatically creating crosstalk-corrected data of a  
2     microarray wherein crosstalk is caused by overlapping dye emission spectra, the system  
3     comprising:

4                   a microarray substrate having three or more calibration dye spots, each of the  
5     calibration dye spots comprising a single pure dye;

6                   an imager having a plurality of output channels wherein for each of the  
7     calibration dye spots the imager generates a dye image containing at least one of the calibration  
8     dye spots for each of the output channels;

9                   means for measuring an output of each of the output channels for each of the  
10    calibration dye spots to obtain output measurements;

11                  means for computing a set of correction factors from the output measurements;  
12    and

13                  means for applying the set of correction factors to quantitation data obtained  
14    from the generated microarray images containing spots having three or more dyes with  
15    excitation or emission spectra to obtain crosstalk-corrected data.

1                   11.     The system as claimed in claim 10 wherein the imager is a microarray  
2 scanner which produces a dye image for each calibration dye spot by scanning the microarray  
3 substrate with a laser of a proper wavelength for the particular dye.

1                   12.     The system as claimed in claim 10 wherein the substrate is a glass slide.

1                   13.     The system as claimed in claim 10 wherein each of the channels is  
2 optimized for a different dye.

1                   14.     The system as claimed in claim 11 wherein the microarray scanner is a  
2 confocal laser microarray scanner.

1                   15.     The system as claimed in claim 10 wherein each of the dyes is a  
2 fluorescent dye.

1                   16.     The system as claimed in claim 10 wherein the means for computing  
2 includes means for computing crosstalk ratios based on spot brightness values for each of the  
3 calibration dye spots on each of the output channels.

1                   17.     The system as claimed in claim 10 wherein the number of calibration dye  
2 spots is more than or equal to the number of dyes.

1                   18.     The system as claimed in claim 10 wherein the calibration dye spots are  
2 hybridized target DNA and fluorescently labeled probe DNA.